Cell Insight 1 (2022) 100015

Contents lists available at ScienceDirect

Cell Insight

journal homepage: www.journals.elsevier.com/cell-insight

Review

Current therapy and development of therapeutic agents for lung cancer

Zilai Wang [a,*], Jiyeon Kim [b], Pin Zhang [a], Jazmin M. Galvan Achi [c], Yuwei Jiang [d], Lijun Rong [c,**]

[a] Chicago BioSolutions, Inc., 2242 W Harrison Street, Chicago, IL, 60612, USA
[b] Department of Biochemistry and Molecular Genetics, University of Illinois at Chicago, Chicago, IL, 60607, USA
[c] Department of Microbiology and Immunology, College of Medicine, University of Illinois at Chicago, Chicago, IL, 60612, USA
[d] Department of Physiology and Biophysics, College of Medicine, University of Illinois at Chicago, Chicago, IL, 60612, USA

ARTICLE INFO

Keywords:
Biomarkers
Immunotherapy
Lung cancer
Non-small cell lung carcinoma
Receptor tyrosine kinases
Receptor tyrosine kinase inhibitors
Small cell lung carcinoma
Small molecule drugs
Targeted therapies

ABSTRACT

In the past decades, great progress has been made for the prevention and treatment of lung cancer. Yet, lung cancer remains as the leading cause of cancer death worldwide. In this manuscript, we describe the current genetic and molecular characterization of lung cancer subtypes, review up-to-date treatment options for lung cancer patients, summarize the antibodies and small molecule drugs under clinical development, and elaborate on the expression and characteristics of important RTK primary targets and representative preclinical agents which may provide new opportunities for lung cancer treatment. Since gefitinib was first introduced to non-small-cell lung carcinoma (NSCLC) patients in 2002, remarkable progress has been made in targeted therapy for NSCLC patients with the development of multiple generations of small molecule inhibitors targeting relevant driver mutations. However, very little achievement has been made in the development of targeted drugs for small-cell lung carcinoma (SCLC). The successful harness of immune checkpoint inhibitors against PD-1/PD-L1 has marked a major advancement in recent lung cancer treatment. Looking forward, therapeutic strategies that tackle brain metastasis are highly desirable, the combination of molecular testing and strategies tailored to tackle tumor heterogeneity and resistance mechanisms is the key direction for future development.

1. Introduction

Lung cancer had been diagnosed in 2.09 million people and resulted in 1.76 million deaths worldwide in 2018, and it's the most common cause of cancer-related death in men and the second most common in women (Bray et al., 2018). It was estimated that 228,820 new cases were diagnosed and 135,720 deaths were resulted from lung cancer in 2020 in the United States (Howlader NKrapcho et al., 2020).

Lung cancer has been grouped into two major types: SCLC and NSCLC. SCLC is a high-grade neuroendocrine (NE) tumor and accounts for about 15% of lung cancers. SCLC has characteristic pathological features including dense sheets of small cells, scant cytoplasm, with fine and granular nuclear chromatin, high mitotic index, earlier development of metastases, and better initial response to chemotherapy and/or radiotherapy (Gazdar et al., 2017). NSCLC account about 85% of lung cancers and has been mainly sub-grouped into lung adenocarcinoma (LUAD), lung squamous-cell carcinoma (LUSC), and large-cell carcinoma (LCC) (Herbst et al., 2018). LUAD accounts for roughly 40% of lung cancer cases, and LUSC represents about 25%–30% of lung cancers (Relli et al., 2019). About 1.3% of lung cancers are LCC (Howlader NKrapcho et al., 2020); LCC refers to a barely differentiated, non–small cell cancer with no specific features of SCLC, adenocarcinoma (ADC), or squamous-cell carcinoma (SQC) (Pelosiet al., 2015). A comprehensive genomic characterization of lung tumors has led to the identification of subtype specific genetic alterations and proposal of eliminating LCC subgroup because it harbors alterations typical of all other subtypes but had no significant signature alterations (Pelosiet al., 2015; Clinical Lung Cancer Genome and Network Genomic, 2013). Because of its unspecified diagnosis on surgical specimens, LCC is often practically termed as NSCLC, not otherwise specified (NSCLC-NOS), and supplemented with comments like “favor ADC” or “favor SQC” if conclusive based on additional immunohistochemistry (IHC) or molecular characterization (Pelosi et al., 2015). In addition to LUAD, LUSC, and the obsolete LCC, there are rare lung cancer subtypes such as adenosquamous carcinoma, sarcomatoid carcinoma, and carcinoid carcinoma (Li and Lu, 2018; Travis et al., 2015; Zheng, 2016), and will not be further discussed in this review.

* Corresponding author.
** Corresponding author. Department of Microbiology and Immunology, University of Illinois at Chicago, 8133 COMRB, 909 S. Wolcott Avenue, Chicago, IL, 60612, USA.
E-mail addresses: zilai.wang@chicagobiosolutions.com (Z. Wang), lijun@uic.edu (L. Rong).

https://doi.org/10.1016/j.cellin.2022.100015
Received 16 November 2021; Received in revised form 10 January 2022; Accepted 17 January 2022
Available online 9 February 2022

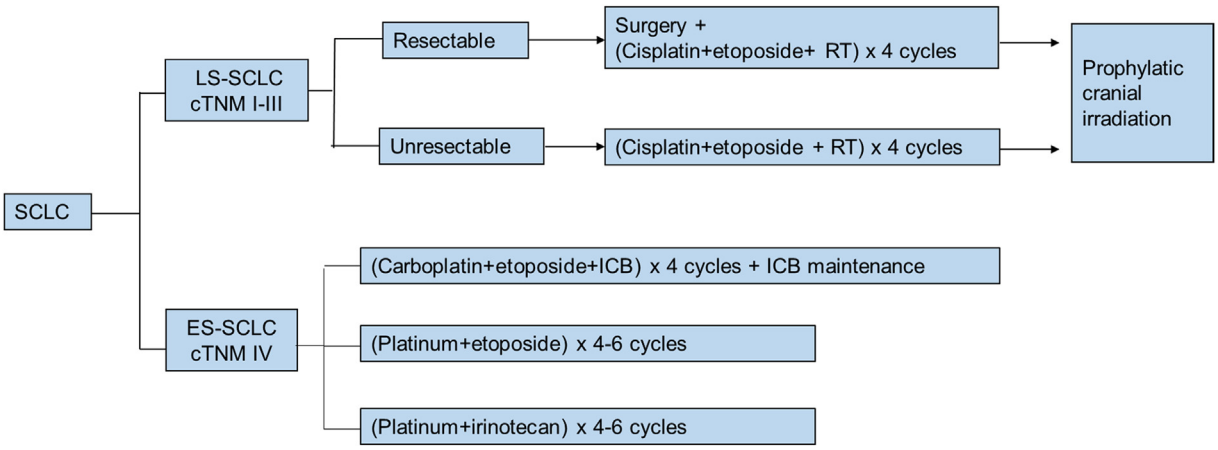

Fig. 1. A summarized schematic outline of the current clinical treatments in SCLC.

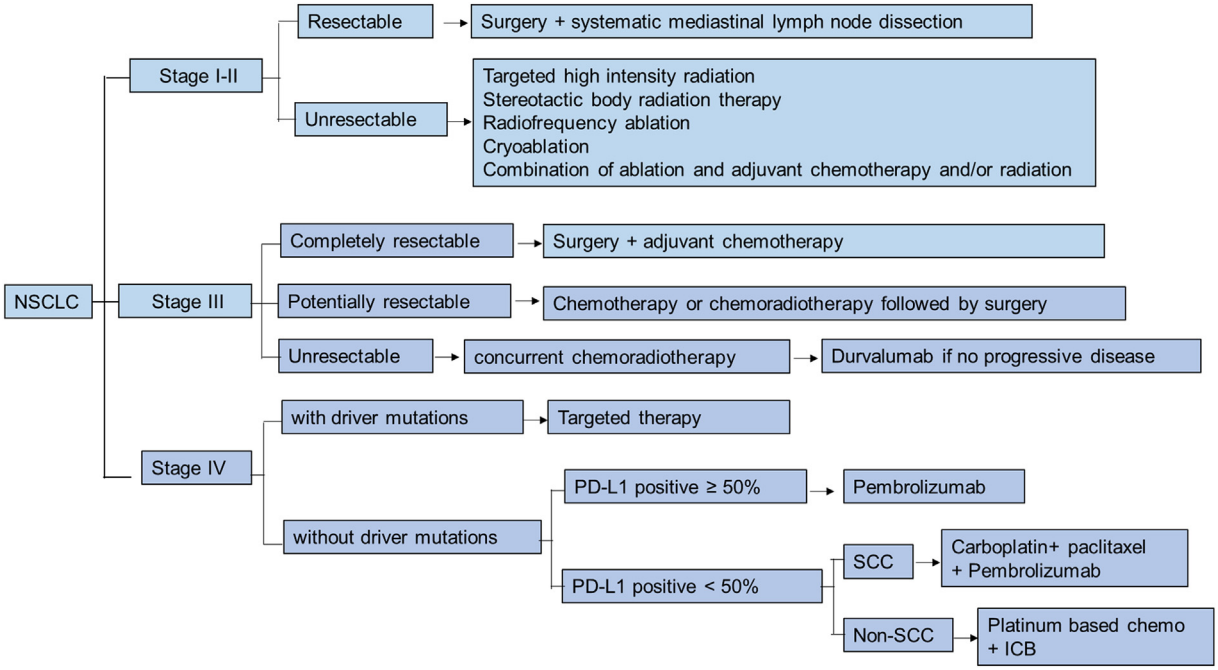

Fig. 2. A summarized schematic outline of the current clinical treatments in NSCLC.

The five-year relative survival rate for lung cancer patients varies depending on the stage at diagnosis, however, the patients are often found at an advanced stage at the time of diagnosis, with 30%–40% of NSCLC cases as stage IV, and about 60% of SCLC cases as stage IV. The staging also provides key information deciding the best treatment options. The most commonly used staging system for NSCLC is the TNM (Tumor, Node, Metastasis) classifications, in which the overall cancer stage is determined after the cancer is assigned a letter or number to characterize the primary tumor size and location (T), the involvement of nearby lymph node (N), and whether the cancer has metastasized (M) to distant organs (Akhurst, 2018). The SCLC has been primarily staged using the Veterans' Administration Lung Study Group (VALSG) two-stage classification scheme as limited or extensive (Kalemkerian, 2012), with limited stage (LS) SCLC confined to the hemithorax of origin, with or without regional lymph-node involvement, which can be safely encompassed in a tolerable radiation field, and extensive stage (ES) SCLC as diseases that have spread beyond the supraclavicular areas and cannot be classified as limited, and may include malignant pleural or pericardial effusions or metastases consistent with hematogenous spread (Kalemkerian, 2012; Argiris and Murren, 2001; Farago and Keane, 2018). The TNM staging system has been proposed and validated by the International Association for the Study of Lung Cancer (IASLC) to be used in place of the VALSG system for SCLC (Shepherd et al., 2007; Vallieres et al., 2009). Under current National Comprehensive Cancer Network (NCCN) guideline, LS-SCLC is defined as TNM stage I-III (T any, N any, M0) but excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan; and ES-SCLC is defined as TNM stage IV (T any, N any, M 1a/bc), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan (NCCN Clinical Practice Guidelines, 2022a). The Surveillance, Epidemiology, and End Results (SEER) program of National Cancer Institute (NCI) routinely uses the Summary Staging system for its cancer data registries and statistics. It classifies cancers into localized, regional, and distant stages. Briefly, if there is no sign that the cancer has metastasized outside of the lung, it is considered localized. Once the cancer has spread outside the lung to nearby structures or lymph nodes, it is classified as regional. When the cancer has

metastasized to distant parts of the body, like the brain, bones, liver, or the other lung lobes, it falls into the distant stage (Howlader NKrapcho et al., 2020). The five-year relative survival rates for SCLC are 27% for localized, 16% for regional, and 3% for distant stage, and merely 6% for all three stages combined. The five-year relative survival rates for NSCLC are: 61% for localized, 35% for regional, and 6% for distant, and 24% for all three combined (Howlader NKrapcho et al., 2020).

Numerous risk factors have been identified for lung cancer (Malhotra et al., 2016). The Lung Cancer Foundation of America (LCFA) outlines that the top 9 risk factors are smoking, exposure to second-hand smoke, radon gas exposure, asbestos exposure, exposure to other carcinogens including radioactive ores, arsenic, and beryllium, drinking water with high arsenic levels, air pollution, previous radiation to lungs, and genetic susceptibility (https://bit.ly/3lRm2Vi). These factors may act singly or jointly with tobacco smoking in shaping the epidemiology landscape of lung cancer. Tobacco smoking is the number one risk factor for lung cancer and is associated with all lung cancer histologic types, with the causal relationship being strongest on SCLC and LUSC, followed by LCC and weakest on LUAD (Khuder, 2001). Tobacco control is now a key measure of the global fight on lung cancer prevention (Herbst et al., 2018). However, about a quarter of lung cancer cases worldwide cannot be attributed to tobacco smoking. There are substantial distinctions in clinical presentation of lung cancers occurred in never-smokers from that of smokers, and in their treatment responses (Sun et al., 2007).

2. Molecular alterations in lung cancer subtypes

Recent genome-wide profiling has greatly increased our understanding of the molecular changes of major lung cancer subtypes (summarized in Table 1).

SCLCs are characterized by their universal loss of the tumor protein 53 (TP53) and retinoblastoma (RB) 1. Loss of function (LOF) mutations in TP53 and RB1 have been shown to affect up to 98% and up to 91% of SCLC, respectively (George et al., 2015). Other recurrent inactivation mutations include NOTCH1 (25%), phosphatase and tensin homolog (PTEN) (9%), cyclin dependent kinase inhibitor 2A (CDKN2A) (5%), and gain of function (GOF) mutations in kit proto-oncogene (KIT) (6%), fibroblast growth factor receptor (FGFR) 1 (6%), c-myc proto-oncogene (MYCC) (6%), n-myc proto-oncogene (MYCN) (4%), myc-related gene from lung cancer (MYCL1) (9%), tumor protein p73 (TP73) (13%), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) (3%) (George et al., 2015). SCLC has been historically recognized as a tumor of neuroendocrine origin, with the characteristic of high expression of achaete-scute complex-like 1 (ASCL1) or neuronal differentiation 1 (NEUROD1) in distinct subset (Gazdar et al., 2017). Recent profiling studies of SCLC from both primary human and mouse tumors support an integrative four molecular subtypes of SCLC defined by expression of four transcription regulators: ASCL1, NEUROD1, pou

Table 2
Biological targets for SCLC and associated biologics and small molecule drugs under ongoing clinical trials.

Biological targets	**Biologics**
PD1	Dostarlimab; Budigalimab (ABBV 181); Tislelizumab (BGB-A317); Camrelizumab (AiRuiKa™); Toripalimab; HLX10; Sintilimab (Tyvyt®); XmAb20717 (bispecific Ab, CTLA-4); tebotelimab (bispecific, LAG-3); AK112 (bispecific, VEGF); AMG404; JS201(bispecific, TGFβ); IBI318 (bispecific, PD-L1)
PD-L1	SHR-1316; LP002; TQB2450; M7824 (bispecific, TGF-βRII), ZKAB001
SSTR2	XmAb18087(bispecific Ab, CD3); PEN-221 (ADC)
DLL3	89Zr-DFO-SC16.56; AMG 757 (bispecific Ab, CD3); BI 764532 (bispecific, CD3); HPN328 (bispecific Ab, CD3)
Fucosyl-GM1	BMS-986012
WT-1	Galinpepimut-S
CTLA-4	ONC-392
	Small molecules
VEGFR	AL3810; Anlotinib; Chiauranib; CM082 (X-82); AL8326; Surufatinib; TT-00420
FGFR	AL3810; Anlotinib; AL8326; Surufatinib; TT-00420
PDGFR	AL3810; Anlotinib; Chiauranib; CM082 (X-82)
c-Kit	Anlotinib; Chiauranib
CSF1R	Chiauranib; CM082 (X-82)
TLR7	BNT411
CDK2	PF-07104091
CDK4/6	Abemaciclib; Trilaciclib
CDK7	SY-5609
AURKA	LY3295668 (AK-01); TT-00420
AURKB	Chiauranib; AZD2811; Barasertib (AZD1152); AL8326; TT-00420
BRD4	PLX2853
c-Myc	RRx-001
EZH1/2	PF-06821497; DS-3201b
WEE1	AZD1775
LSD1	CC-90011; SYHA1807
TIGIT	Tiragolumab
TP53	ALRN-6924
PARP 1/2	Fluzoparib (SHR-3162); Senaparib (IMP4297); Rucaparib; Veliparib (ABT-888); AZD5305
ATM	Elimusertib
ATR	AZD6738; Berzosertib
BCL-2 family	Navitoclax; APG-1252; Venetoclax
IAPs	LCL-161
SMO	ZSP1602
TOPO	SN-38; PLX038; CBX-12; EP0057
TROP2	SKB264
DPP	BXCL701
DNA	Lurbinectedin (PM01183); Doxil

*ADC, antibody drug conjugate.

Table 1
A brief summary of frequent gene mutations in lung cancer.

Frequent gene mutations in SCLC	
TP53	98%
RB1	91%
NOTCH1	25%
PTEN	9%
CDKN2A	5%
TP73	13%
MYCL1	9%
FGFR1	6%
KIT	6%
MYCC	6%
MYCN	4%
PIK3CA	3%

LUAD frequent mutations in key pathways	
RTK/RAS/RAF pathway	76%
Cell cycle regulators	64%
P53 pathway	63%
Chromatin and RNA splicing factors	49%
PI3K-mTOR pathway	25%
Oxidative stress pathway	22%

Frequent gene mutations in LUAD	
TP53	46%
KRAS	32%
EGFR	27%
KEAP1	17%
STK11	17%
NF1	11%
MET	7%
PIK3CA	7%
CDKN2A	4%
RB1	4%
RIT1	2%

Frequent gene mutations in LUSC	
TP53	81%
MLL2	20%
AKT3	16%
PIK3CA	16%
CDKN2A	15%
NFE2L2	15%
KEAP1	12%
PTEN	8%
NOTCH1	8%

class 2 homeobox 3 (POU2F3) and yes associated protein 1 (YAP1) (Rudin et al., 2019).

Recurrent mutations in key pathways and processes characterize LUAD. Among these are receptor tyrosine kinase (RTK)/RAS/RAF pathway activation (76%), phosphatidylinositol-3-kinase (PI3K)- mechanistic target of rapamycin (mTOR) pathway activation (25%), p53 pathway mutations (63%), mutations of cell cycle regulators (64%), mutations of oxidative stress pathways (22%), and alterations of various chromatin and RNA splicing factors (49%). Gene fusions involving anaplastic lymphoma kinase (ALK) (3/230 cases), ros proto-oncogene 1 (ROS1) (4/230) and rearranged during transfection (RET) (2/230) have also been identified (Cancer Genome Atlas Research, 2014). Common somatic mutations of oncogenes and tumor suppressors in LUAD include TP53 (mutated in 46% of cases), epidermal growth factor receptor (EGFR) (27%), kirsten rat sarcoma viral oncogene homolog (KRAS) (32%), kelch like ech associated protein 1 (KEAP1) (17%), serine/threonine kinase 11 (STK11) (17%) and neurofibromin 1 (NF1) (11%), RB1 (4%), CDKN2A (4%), BRAF (10%), PIK3CA (7%), met proto-oncogene (MET) (7%) and the small GTPase gene ras-like without caax protein 1 (RIT1) (2%). Importantly, mutations in KRAS are almost mutually exclusive with those in EGFR (Cancer Genome Atlas Research, 2014).

LOF mutations in LUSC were identified in tumor suppressor genes such as TP53 (mutated in 81% of cases), MLL2 (20%), CDKN2A (15%), KEAP1 (12%), PTEN (8%), and NOTCH1 (8%). In contrast, GOF mutations affected oncogenes such as PIK3CA (16%), AKT3 (16%) and nuclear factor erythroid 2-related factor 2 (NFE2L2) (15%). Frequent copy number alterations have been observed in sry-box 2 (SOX2), platelet derived growth factor receptor alpha (PDGFRA), EGFR, FGFR1 and cyclin d1 (CCND1). Deletions were identified in tumor suppressors such as CDKN2A, PTEN and NF1 (Cancer Genome Atlas Research, 2012).

A genomic study of 1255 lung tumors with clinical annotations of all histological subgroups has revealed genetic alterations that preferentially occurred in a certain subtype (Clinical Lung Cancer Genome and Network Genomic, 2013), such as mutations of ALK (3.4%), BRAF (2.7%), EGFR (15.3%), erb-b2 receptor tyrosine kinase 2 (ERBB2) (1.7%), KRAS (32.6%), and STK11 (17.4%) in LUAD; copy number gain of MYCN (6.5%) in SCLC; and alterations in DDR2 (1.1%), FGFR3 (0.8%), and NFE2L2 (10.6%) in LUSC. The original assigned LCC group was found to contain mutations typical of all other subtypes with no significant signature alterations (Clinical Lung Cancer Genome and Network Genomic, 2013). One clinically significant subtype is "large-cell neuroendocrine carcinoma" (LCNEC), which has been previously included in LCC by histopathology. LCNEC was found to exhibit substantial transcriptional similarity to SCLC, and several key genes like TP53, RB1 and EP300 that are frequently altered in SCLC are also significantly mutated in LCNEC (Clinical Lung Cancer Genome and Network Genomic, 2013). Another genomic profiling study revealed distinct molecular changes in LCNECs, while certain mutations (e.g., RB1, MYCL1) resemble changes found in SCLC, others are typical of LUAD or LUSC (e.g., STK11, KEAP1, NKX2-1, RAS, BRAF, and NFE2L2). Thus, LCNEC may be classified into a molecularly defined subset of tumors with overlapping alterations to other major lung cancer subtypes (Clinical Lung Cancer Genome & Network Genomic, 2013; George et al, 2018).

3. Current therapy for SCLC

Please refer to Fig. 1 for a summarized schematic outline of the current clinical treatments in SCLC. At disease presentation, about 30% of cases with SCLC are diagnosed as LS-SCLC or as M0 by the TNM system, with their tumors confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes; about two-thirds of patients with SCLC would have clinical evidence of metastases that have spread beyond the supraclavicular area and are designated as ES-SCLC (Farago and Keane, 2018; Wang et al., 2019).

Because SCLC often found to metastasize early on during disease progression, and because they are readily responsive to chemotherapy and/or radiotherapy, surgery is not often practiced in this disease. However, it was reported that in small, asymptomatic, and node-negative SCLC, better survival was achieved when surgical removal was performed prior to chemotherapy (Shepherd, 2010).

For LS-SCLC, joint chemotherapy (including cisplatin and etoposide, or carboplatin and etoposide) is often provided in combination with concurrent chest radiotherapy (RT). According the latest NCCN guideline, four cycles of chemotherapy with cycle length of every 21–28 days with concurrent RT are recommended. For ES-SCLC, the preferred regimens are platinum-based chemotherapy (typically with carboplatin or cisplatin plus etoposide) in combination with immunotherapy with atezolizumab or durvalumab in 4–6 cycles; regimens only involve platinum based chemotherapy are also under current NCCN recommendations (NCCN Clinical Practice Guidelines, 2022a).

The role of immune checkpoint blockade (ICB) for programmed cell death-1 (PD-1) or programmed death-ligand 1 (PD-L1) in frontline treatment of patients with ES-SCLC has been well established. Two PD-L1 antibodies, atezolizumab and durvalumab, were shown to prolong the overall survival (OS) when used in combination with platinum-based drugs and etoposide, compared to the same chemotherapy regimen alone (Horn et al, 2018; Paz-Ares et al, 2019). In a double-blind, placebo--controlled, randomized, phase III trial (NCT02763579) (Horn et al., 2018), Horn et al. evaluated the effect of four cycles of carboplatin and etoposide with either atezolizumab or placebo followed by either atezolizumab or placebo until study endpoint, and showed that atezolizumab treatment prolongs the median OS from 10.3 months in the placebo group to 12.3 months in the study group, and prolongs the median progression-free survival (PFS) from 4.3 months for the placebo group to 5.2 months for the atezolizumab group (Horn et al., 2018). This led to the FDA approval of atezolizumab to be added to the platinum based first line treatment regimen for patients with ES-SCLC in 2019. It was followed by the FDA approval of durvalumab in 2020 for results reported in the CASPIAN trial (Paz-Ares et al., 2019; Ragavan and Das, 2020).

Bain metastases are very common in patients of SCLC, with an incidence of about 18% at diagnosis and increase dramatically to about 80% at 2 years, and about 59% of SCLC patients indeed die with or from active metastases in their central nervous system (CNS) (Slotman et al., 2007). It's generally recommended that patients who have a complete remission after chemotherapy to take prophylactic cerebral irradiation (PCI). Slotman et al. (2007) reported in a randomized trial in patients with ES-SCLC that PCI can reduce the incidence of symptomatic brain metastases within 1 year from 40.4% in the control group compared to 14.6% in the irradiation group, and increases 1 year survival from 13.3% in the control group to 27.1% in the irradiation group.

When relapse does occur, current standard of care recommends that patients who relapse after 6 months from initial treatment to be treated again with the same chemotherapy regimen. For patients who relapse in less than 6 months, it's recommended to use either topotecan or paclitaxel as second-line mono-therapy (Qin and Kalemkerian, 2018). Lurbinectedin, a novel anticancer drug that inhibits transcription and induces DNA double-strand breaks, showed significant safety advantage when compared with topotecan, and has been approved by Food and Drug Administration (FDA) in 2020 for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy (Farago et al., 2019; Kepp et al., 2020).

Hipp et al. (Hipp et al., 2020) reported a novel IgG-like T-cell engaging bispecific antibody (ITE) that potently targets T-cells to attack SCLC cells expressing Delta-like ligand 3 (DLL3), a cell surface protein that is highly expressed in SCLC cells but not normal cells. They showed that binding of DLL3/CD3 ITE to DLL3-positive tumor cells and T-cells induces tumor cell lysis and activation of T-cells *in vitro*, and increased infiltration of T-cells into the tumor tissue, and apoptosis of the tumor cells and tumor regression in a human T-cell engrafted xenograft model (Hipp et al., 2020). Currently there are multiple clinical trials exploring the bispecific antibodies targeting both DLL3 and CD3 T-cells in SCLC patients (89Zr-DFO-SC16.56 (NCT04199741); AMG 757 (NCT03319940); BI 764532 (NCT04429087); HPN328 (NCT04471727)).

Many small molecule drugs for SCLC are currently under clinical evaluation. AL3810, a multi-tyrosine kinase inhibitor with potent anti-angiogenic and anti-tumor activity via targeting VEGFR, FGFR and PDGFR, is under a phase II/III study to evaluate its safety and tolerability and efficacy in combination with carboplatin plus etoposide in untreated participants with ES-SCLC (NCT04254471). Another multi-kinase inhibitor, CM082, which targets VEGFR, PDGFR, and CSF1R, is being evaluated in a single-arm, multi-center, phase II study for its efficacy and safety in combination with JS001 (a PD-1 antibody) as the second-line treatment of advanced SCLC (NCT03904719). The nearly universal loss of TP53 and RB1, which are key regulators of genome instability and cell cycle progression, may make SCLC tumors particularly susceptible to DNA damage. This has sparked continuous interests on agents targeting DNA damage repair and cell cycle checkpoints for SCLC. Small molecule inhibitors targeting cell cycle mechanisms, such as CDK4/6 inhibitors abemaciclib and trilaciclib, and Aurora kinase B inhibitors chiauranib, AZD2811 and AZD1152, are currently under clinical investigation. Cyclin-dependent kinase 7 (CDK7) was identified as a potential therapeutic target for SCLC through its covalent inhibitor THZ1 in a screen study of over 1000 experimental and clinical compounds (Christensenet al., 2014). Follow-up studies further indicated that CDK7 inhibition would disrupt cell-cycle progression and induce DNA replication stress and genome instability preferentially in SCLC and promote proinflammatory immune response (Zhang et al., 2020). Several CDK7 inhibitors have been exploited in preclinical SCLC models with anti-cancer efficacy (Choi et al., 2021; Christensen et al., 2014; Zhang et al., 2020), and SY-5609 is under active clinical evaluation (NCT04247126). In addition, inhibitors for DNA damage and repair pathways are heavily investigated. Fluzoparib (SHR-3162), a PARP inhibitor, is in a phase Ib study in combination with SHR-1316 (anti-PD-L1) in SCLC patients (NCT04041011). Other PARP inhibitors have also been reported in clinical trials for SCLC patients (IMP4297 (NCT04434482); rucaparib (NCT04209595); veliparib (NCT03227016)). As listed in Table 2, various biological targets for SCLC are being exploited for their therapeutic potential in SCLC patients.

4. Current therapy for NSCLC

Please refer to Fig. 2 for a summarized schematic outline of the current clinical treatments in NSCLC. Since early NSCLCs are often localized and are more resistant to chemotherapy and/or radiation, surgery has been the treatment of choice. For small, inoperable tumors, several treatment options are available: 1) targeted high intensity radiation; 2) stereotactic body radiation therapy; 3) radiofrequency ablation; 4) cryoablation; 5) combination of ablation and adjuvant chemotherapy and/or radiation (Dupuy and Shulman, 2010; Non-small Cell Lung Cancer Collaborative, 2000; Bargellini et al., 2011; Abel et al., 2019).

For patients with advanced NSCLC, there is a wide variety of treatment options, including traditional chemotherapies that broadly target all rapidly dividing cells, and targeted reagents that are designed to specifically act on aberrations associated with a person's tumor. Molecular markers are now routinely profiled for NSCLC tumors to guide future treatment option. Mutations in EGFR, ALK, BRAF, HER2, MET, RET, ROS1, and neurotrophic receptor tyrosine kinase (NTRK) have been well established to have impacts on patient treatment and drug response (Black and Khurshid, 2015). Molecular targeted therapies have been extensively practiced for a subset of LUAD patients who are mostly young and never-smokers. For patients with advanced NSCLC who would not benefit from an approved molecular targeted therapy, platinum-based chemotherapy (typically carboplatin or cisplatin plus pemetrexed) in combination with immunotherapy are the current preferred treatment irrespective of histology and PD-L1 levels. For advanced NSCLC patients with strongly positive expression of PD-L1 ($\geq$50%) and negative for actionable molecular biomarkers, anti-PD-1/PD-L1 immunotherapy (pembrolizumab, atezolizumab, or cemiplimab) is the preferred treatment (NCCN Clinical Practice Guidelines, 2022b) (Fig. 2).

5. Molecular targeted therapy

While recent progress in immunotherapy has greatly re-shaped the treatment landscape of NSCLC, targeted therapy remained as a cornerstone of NSCLC management and has significantly improved patient outcomes and quality of life. We summarize the present biological targets for NSCLC and their antibodies and small molecule inhibitors under active clinical evaluation in Table 3.

5.1. EGFR

Lung cancer associated EGFR mutations occur in 15–20% of patients with LUAD and are most commonly detected in nonsmokers and patients of Asian ethnicity. These mutations frequently located in the catalytic tyrosine kinase domain of EGFR, such as small in-frame deletion in exon 19 (E19del), and leucine-to-arginine point mutation at codon 858 (L858R) within exon 21, result in constitutively activated receptor function (O'Leary et al., 2020). Gefitinib, the first EGFR specific tyrosine kinase inhibitor (TKI), was tested in EGFR-expressing NSCLC, but tumor responses were only observed in a subset of patients with chemotherapy-refractory advanced NSCLC (Fukuoka et al., 2003). Lynch et al. (Lynch et al., 2004) demonstrated that only the tumors with somatic mutations in the tyrosine kinase domain of the EGFR gene respond to gefitinib. Erlotinib, another first-generation reversible EGFR TKI was later demonstrated to be beneficial for NSCLC patients after the failure of first-line or second-line chemotherapy (Shepherd et al., 2005). Having established in first-line clinical trials, gefitinib and erlotinib are now first-line treatments for NSCLC patients with EGFR E19del or L858R mutations (Mitsudomi, 2010; Rosell, 2012; Zhou et al., 2011). Afatinib and dacomitinib are second-generation irreversible EGFR TKI with pan-ErbB family inhibitory activity with broad-spectrum antitumor activity against EGFR mutations, and both have been tested and approved for the treatment of EGFR-mutated NSCLC in the first-line setting (Yang et al., 2015a; Wu et al., 2017). EGFR T790M mutation was first reported for gefitinib resistance in an NSCLC patient in 2005 (Kobayashi et al., 2005). A later study further identified that the T790M mutation occurs in 0.7% of all NSCLC cases (Graham et al., 2018), and it accounts for about 50% of all cases with resistance to gefitinib and erlotinib (Hata et al., 2015). Osimertinib, along with other third-generation TKIs, were developed to selectively and irreversibly target T790M mutations. Osimertinib was shown to have increased selectivity for exon 19, L858R, and T790M mutations over wild-type EGFR, thus with an improved off-target toxicity profile (Cross et al., 2014). Osimertinib is a preferred choice for treating patients with EGFR-mutated NSCLC over first- and second-generation EGFR TKIs for its effectiveness against the EGFR T790M mutation in addition to EGFR TKI sensitizing mutations, lower frequency of CNS metastasis, longer PFS and less serious adverse events (Mok et al., 2017; Soria et al., 2018). In addition to osimertinib, almonertinib (HS-10296), another third-generation EGFR TKI that targets both EGFR-sensitizing and T790M resistance mutations, has been evaluated in a phase I study to be safe and effective for patients with locally advanced or metastatic NSCLC with EGFR T790M mutation (NCT0298110) (Yang et al., 2020). Almonertinib was shown to have progression-free survival benefit in EGFR T790M positive NSCLC patients who had progressed after previous EGFR-TKI treatment, especially with efficacy against CNS metastases in an open-label, single-arm, phase II study (NCT02981108) (Shun Lu et al., 2020). Almonertinib has been approved in China to treat advanced EGFR T790M positive NSCLC in 2020. In addition to osimertinib and almonertinib, Nagasaka et al. (2020) have summarized the late-stage clinical development of a list of third-generation EGFR TKIs (e.g., lazertinib, alflutinib, rezivertinib, ASK120069, SH-1028, D-0316 and abivertinib) of their interim results of phase I-III trials.

Despite the successful clinical application of third-generation TKIs, mutations conferring resistance to third-generation TKIs have been identified alongside the T790M mutation, such as C797S in exon 20 (*63*), as well as other tertiary mutations include L798I, L718Q, L692V, E709K,

Table 3
Biological targets for NSCLC and associated biologics and small molecule drugs under ongoing clinical trials.

Biological targets	**Biologics**
EGFR	Necitumumab; Amivantamab (bispecific, c-MET); EMB-01 (bispecific, c-MET); JMT101; Lazertinib (YH25448); SCT510; SI-B001; M1231(bispecific, MUC1)
HER3	SI-B001; TY 9591; MCLA-128 (bispecific, HER2); Patritumab deruxtecan (U3-1402) (ADC)
HER2	MCLA-128 (bispecific, HER3); RC48 (ADC)
MET	Emibetuzumab (LY2875358); Amivantamab (bispecific, EGFR); EMB-01 (bispecific, EGFR); REGN5093 (bispecific, xMET); Telisotuzumab vedotin (ABBV-399; ABT 399) (ADC)
VEGFR2	Ramucirumab
AXL	BA3011 (ADC)
ROR2	CAB-ROR2-ADC
PD-L1	AK105; CS1001; GEN1046 (bispecific, 4-1BB); KN046 (bispecific, CTLA-4); MEDI4736; Bintrafusp alfa; INCB086550; M7824 (MSB0011359C); Atezolizumab (MPDL3280A); SHR-1316; SHR 1701; TQB2450
PD1	Prolgolimab (BCD 100); Camrelizumab; Sintilimab; Dostarlimab; Toripalimab; GNR-051; Sintilimab (IBI308); Spartalizumab (PDR001); PF-07209960; AK112 (bispecific, VEGF); Penpulimab (AK105); SHR-1210; Toripalimab; BI 754091; Camrelizumab (SHR-1210); Pembrolizumab (MK-3475); CDX-527 (bispecific, CD27); Cemiplimab (LIBTAYO®; cemiplimab-rwlc); JS001; Sintilimab (Tyvyt®); PDR001; Dostarlimab; Zimberelimab; Genolimzumab (GB226); HX008; IBI308; JTX-4014; TSR-042; Nivolumab (ONO-4538/BMS-936558); Sasanlimab (PF-06801591); Cemiplimab (REGN2810); Retifanlimab (previously known as MGA012); RO7121661 (bispecific, Tim3); RO7247669; Sasanlimab (PF-06801591); SCT-I10A; REGN2810 (Cemiplimab); Spartalizumab; Tislelizumab (BGB-A317); Toripalimab; Zimberelimab (AB122); AK104 (bispecific, CTLA-4)
IL1RAP	CAN04
MUC1	M1231 (ADC)
TIM3	Cobolimab; RO7121661 (bispecific, PD1)
CD47	DSP107
4-1BB	DSP107; GEN1042 (BNT312)(bispecific, CD40); GEN1046 (bispecific, PD-L1)
CTLA-4	Tremelimumab (ticilimumab, CP-675,206); Ipilimumab; KN046 (bispecific, PD-L1); Quavonlimab; AK104 (bispecific, PD1); ONC-392
TGF-β	Fresolimumab; M7824 (MSB0011359C); SHR 1701
ANG2	BI 836880 (Bispecific, VEGF)
VEGF	Bevacizumab; GB-222; TRS 003; ABP 215 (MVASI™); AK112 (bispecific, PD1); BI 836880 (bispecific, Ang2); CT-P16; BAT1706; MIL 60; PF-06439535
CD40	GEN1042 (BNT312) (bispecific, 4-1BB)
CD3	GEN1044 (bispecific, 5T4)
5T4	GEN1044 (bispecific, CD3)
TIGIT	IBI939; MK-7684; Vibostolimab; Tiragolumab; BGB-A1217; AB154
TNFα	Infliximab
LPAM	Vedolizumab
CD73	Oleclumab (MEDI9447); CPI-006
LAG3	BI 754111
ILT4	MK-4830
IL15	PF-07209960; ALT-803
sCLU	AB-16B5
IL6	Tocilizumab
CD27	CDX-527 (bispecific, PD1); MK-5890
CEACAM1	CEACAM1
EDB	Darleukin (L19IL2)
NKG2A	Monalizumab (IPH2201)
CFH	GT 103
ICOS	Vopratelimab; KY1044
S15	NC318
CD105	TRC105 (carotuximab)
PTK7	Cofetuzumab pelidotin (ADC)
TROP2	DS-1062a (ADC); SKB264
Mesothelin	LMB-100 (ADC)
FRα	MORAb-202 (ADC)
CEACAM5	SAR408701 (ADC)
ITGB6	SGN-B6A (ADC)
STn	SGN-STNV (ADC)
	Small molecules
EGFR	Brigatinib; Abivertinib; Alflutinib (AST2818); HS-10296 (Almonertinib); ASK120067; Avitinib; Osimertinib (AZD9291); Icotinib (Conmana); BPI-7711; CK-101 (RX518); CKD-702; CLN-081 (TAS6417); D 0316; DZD9008; Nazartinib (EGF816); Almonertinib (HS-10296); Poziotinib; SH-1028; TAK-788; Tarloxotinib bromide (TH-4000); TQB3456; Dacomitnib; XZP-5809-TT1; YH25448; ZN-e4; Mobocertinib
pan EGFR	Sapitinib (AZD8931); FCN-411; Pyrotinib
HER2	Tarloxotinib bromide (TH-4000)
PDGFR	Lucitanib; Anlotinib; CM082; Famitinib (SHR1020); Nintedanib
FGFR	Lucitanib; Anlotinib; AZD4547; Erdafitinib; Nintedanib; Rogaratinib
MET	Sitravatinib; APL-101; Cabozantinib; Capmatinib (INC280); CKD-702; CT053PTSA; Glesatinib; Merestinib; Savolitinib (AZD6094, HMPL-504, volitinib); Crizotinib (PF-02341066); PLB1001; Tepotinib
ALK	Brigatinib; Alectinib (Alecensa); APG-2449; PF-06463922; Avitinib; Ceritinib; DS-1205c; Entrectinib; Crizotinib (PF-02341066); Lorlatinib (PF-06463922); PLB1003; TQ B3101; TQ-B3139; WX-0593; Ensartinib (X-396)
BTK	Abivertinib; Ibrutinib (Imbruvica®)
AXL	Bemcentinib; BGB324; Cabozantinib; CT053PTSA; Glesatinib; Dubermatinib (TP-0903)
VEGFR2	Lucitanib; Sitravatinib; Lenvatinib; Anlotinib; Cabozantinib; CM082; CT053PTSA; Famitinib (SHR1020); Fruquintinib (Elunate®); Nintedanib; Vandetanib
cKIT	Famitinib (SHR1020)
NTRK	Taletrectinib (DS-6051b/AB-106); BAY2757556 (Larotrectinib)
ROS1	Taletrectinib (DS-6051b/AB-106); APG-2449; PF-06463922; Entrectinib; Lorlatinib (PF-06463922); WX-0593
RET	BOS172738; Cabozantinib; LOXO-292; Pralsetinib; Selpercatinib (RETEVMO™); TAS0953/HM06; TPX-0046
MER	CT053PTSA
FLT3	CT053PTSA
IL-15Rα	ALT-803

(*continued on next page*)

Table 3 (*continued*)

Biological targets	**Biologics**
CR3	beta-glucan MM-10-001
CD40	APX005M
TAM	Sitravatinib
CXCR1	Navarixin (SCH 527123)
CXCR2	QBM076; Navarixin (SCH 527123)
LAG3	MK-4280
A2AR	AZD4635 (HTL1071); Etrumadenant; NIR178; PBF-1129; PBF-509 (Taminadenant, NIR178)
EP4	Grapiprant
RXR	IRX4204
ALK4/5	Vactosertib (TEW-7197, EW-7197)
ER	Fulvestrant
LXR	RGX-104
TLR-7	TQ-A3334
CD122	NKTR-214
RORγ	LYC-55716 (Cintirorgon) (LY55716)
PI3K	Copanlisib (Aliqopa™); Eganelisib (IPI-549) (PI3Kγ); Idelalisib
AKT	AZD5363; Ipatasertib
FAK	APG-2449; Defactinib (VS-6063, PF-04554878)
KRAS	Sotorasib (AMG 510); GDC-6036; MRTX849
JAK1	Itacitinib
SHP2	JAB-3068; JAB 3312; RMC-4630; TNO155
SHP1	SC-43
MEK	Selumetinib; Binimetinib; Trametinib; HL-085; MEK162; Mirdametinib (PD0325901); RO5126766 (CH5126766); VS-6766
ERK1/2	HH2710
mTOR	Vistusertib (AZD2014); Sapanisertib
RAF	Donafenib; Encorafenib
CDK4/6	Abemaciclib; Palbociclib; G1T38; GLR2007
MDM2	APG-115
HDAC6/3	Citarinostat (ACY-241, HDAC-IN-2)
HDAC	Panobinostat; Entinostat
BET	JAB-8263
ATR	Berzosertib (VE-822, VX-970, M6620); AZD6738
PARP	Niraparib (Zejula®); Pamiparib (BGB-290); Rucaparib; AZD5305; RP12146
BCL-2	APG-1252; Navitoclax
IAPs	DEBIO 1143 (AT-406, SM-406)
IDO	Epacadostat
Aromatase	Anastrozole; Letrozole
IL1b	Canakinumab (ACZ885, Ilaris)
NAE	Pevonedistat (TAK-924/MLN4924)
GLS	DRP-104; Telaglenastat (CB-839);
NOS	L-NMMA
CDA	Tetrahydrouridine
MOZ	PF-07248144
XPO1	Selinexor
FTase	Tipifarnib
MNK-1/2	Tomivosertib
Microtubule	ABRAXANE; Vinorelbine

*ADC, antibody drug conjugate.

L844V, and G796D (O'Leary et al., 2020; Thress et al., 2015; Zheng et al., 2017). A more comprehensive survey of the diverse landscape of EGFR resistance mechanisms and mutations has been summarized elsewhere (Kobayashi & Mitsudomi, 2016; Tumbrink, Heimsoeth, & Sos, 2021). Uncommon EGFR mutations account for approximately 10%–20% of cases of EGFR mutation-positive NSCLC. Among them, the "major" variants include exon 20 insertions, exon 18 G719X, exon 20 S768I, and exon 21 L861Q Mutations (Gristina et al., 2020; Passaro et al., 2021). Yang and colleagues reported the activity of afatinib in patients with EGFR S768I, L861Q, and G719X mutations from a pooled analysis of three clinical trials, LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6 (Yang et al., 2015b), and this led to the FDA approval of afatinib as a first line therapy of NSCLC patients with S768I, L861Q, and/or G719X mutations in 2018. Amivantamab, an Fc enhanced EGFR/cMet bispecific antibody, was shown to have durable responses with tolerable safety in the CHRYSALIS trial and now is an approved treatment in patients with EGFR exon20 insertions whose disease has progressed on or after platinum-based chemotherapy (Park et al., 2021; Syed, 2021). Mobocertinib, a new inhibitor targeting EGFR exon20 insertions, has been evaluated in a phase I/II dose-escalation/expansion trial (NCT02716116) and demonstrated antitumor activity in patients with diverse EGFR exon20 insertion variants (Riely et al., 2021).

5.2. *ALK*

ALK gene rearrangements in NSCLC usually consist in fusion with the echinoderm microtubule-associated protein like 4 (EML4) gene resulted from chromosome inversion, causing the abnormal expression and activation of ALK in the cancer cells (Soda et al., 2007). The EML4-ALK fusion gene has been implicated in approximately 2–7% of NSCLC, with majority of cases as LUAD. Rearrangements of the ALK gene with partner genes other than EML4 have been described. So far, 27 variants of ALK fusion have been reported (Katayama et al., 2015). Crizotinib, a kinase inhibitor for ALK/ROS1/MET, has been shown for its clinical efficacy in treating NSCLC patients harboring EML4-ALK gene fusion (Kwak et al., 2010). Relapse usually occurs within 1–2 years for patients treated with crizotinib; regardless of the presence of CNS involvement at beginning, CNS is the most frequent site of relapse or progression with various mechanisms of acquired resistance (Katayama et al., 2015; Doebele et al., 2012). Second-generation ALK TKIs, including ceritinib and alectinib, are

valuable treatment alternatives to chemotherapy when crizotinib fails, because of their higher inhibitory potency to the wild-type fused ALK protein, better affinity, and improved penetrance to the CNS (Katayama et al., 2015; Friboulet et al., 2014). Resistance to second-generation ALK inhibitors often occurs due to secondary ALK mutations. For example, the frequency of ALK G1202R mutation increases significantly after treatment with second-generation agents (Gainor et al., 2016). Lorlatinib, a third generation ALK/ROS1 inhibitor, has been trialed in advanced NSCLC patients with ALK-positive or ROS1-positive mutations who had CNS metastases and previously two or more TKI treatments, and showed both systemic and intracranial activity (Shawet al., 2017). Alectinib, brigatinib, and lornatinib are the current three first line therapy for ALK rearrangement positive NSCLC (Clinical Practice Gu, 2022b). Mechanisms for lorlatinib resistance are currently under investigation, including new compound mutations and alternative signaling routes.

5.3. ROS1

ROS1 gene rearrangements are observed in 1–2% of NSCLC. Nine fusion protein of ROS1 variants have been identified in NSCLC (Bergethon et al., 2012). Both crizotinib and entrectinib have been approved by the FDA to be used in NSCLC patients with ROS1 rearrangement, with entrectinib showed greater activity against intracranial disease (Shaw et al., 2014; Araujo et al., 2020). Acquired resistance to these TKIs has been identified as secondary mutations such as ROS1 G2032R solvent front mutation, L2026M gatekeeper mutation, or by alternative signaling (Awad et al., 2013; Papadopoulos et al., 2020). Taletrectinib (DS6051b/AB-106), a highly selective type I ROS1/NTRK inhibitor with potent preclinical activity against both ROS1 G2032R and L2026M mutations, has been evaluated in a multicenter, nonrandomized, open-label, multiple-dose trial, and shown to have manageable toxicities and preliminary confirmed clinical activity in patients with crizotinib-refractory ROS1 positve NSCLC(84). Currently, a global phase II, multicenter, single-arm, open label study of taletrectinib in patients with ROS1 positive NSCLC is ongoing in United States (NCT04919811), and another large-scale phase II clinical trials investigating the clinical efficacy of taletrectinib in patients with TKI-naïve and TKI-refractory ROS1 positive NSCLC is ongoing in China (NCT04395677). More ROS1 inhibitors, including ceritinib, cabozantinib and lorlatinib, are under active evaluation. Repotrectinib, a rationally designed, macrocyclic TKI that is selective and highly potent against ROS1, TRKA-C, and ALK, has demonstrated preliminary clinical activity against patients with crizotinib-refractory ROS1 positive NSCLC (Drilon et al., 2018).

5.4. MET

MET is an attractive target for the treatment of lung cancer. MET receptor tyrosine kinase overexpression, amplification, and activating mutations have been implicated in specific subsets of lung tumors. MET activating mutations occur in about 7% of LUADs, MET amplification occurs in about 4% of LUADs and 1% of LUSCs (Cancer Genome Atlas Research, 2014; Gelsomino et al., 2014). MET exon 14 skipping, which causes disruption of its ubiquitin-mediated degradation and thus increased MET protein levels, is a critical event for metastasis and has been observed in about 3% LUADs and around 2% in other lung neoplasms (Reungwetwattana et al., 2017). At least five MET-targeted TKIs are being clinically evaluated for patients with MET exon 14 skipping-NSCLC, including crizotinib, cabozantinib, capmatinib, tepotinib, and glesatinib (*87*). Capmatinib is the first FDA-approved therapy to treat NSCLC with MET exon 14 skipping for its high selectivity for MET over other kinases and it is active against MET overexpression, MET amplification, MET exon 14 skipping mutations, or MET activation due to high expression of its ligand hepatocyte growth factor (HGF) (Baltschukat et al., 2019). Tepotinib, a highly selective oral MET inhibitor, has been approved in 2020 in Japan, and in 2021 in United States, for NSCLC patients harboring MET alterations (Markham, 2020).

5.5. NTRK

NTRK gene fusions occur in less than 0.5% of NSCLC tumors, with higher frequency be observed in non-smoking LUAD patients. Larotrectinib has been approved for the treatment of patients with advanced or metastatic tumors that harbor an NTRK gene fusion without a known acquired resistance mutation (Haratake and Seto, 2020). Larotrectinib was the first-in-class TRK inhibitor received accelerated approval for patients of all ages with solid tumors harboring NTRK fusions (Larotrectinib OK'd for Cancers with TRK Fusions, 2019). Entrectinib was the second TRK inhibitor to receive such tissue-agnostic approval (Entrectinib OK'd for Cancers with NTRK Fusions, 2019). In addition, new generations of TRK inhibitors, such as taletrectinib, selirectinib, and repotrectinib, are currently under active clinical evaluation.

5.6. AXL

AXL, a TAM (TYRO3, AXL, and MERTK) family receptor tyrosine kinase, has been repeatedly identified as a contributing factor to the resistance of targeted therapies. Zhang et al. (2012) reported increased expression and activation of AXL in both erlotinib resistant human NSCLC cell lines and primary tumors, and genetic or pharmacological inhibition of AXL can restore sensitivity to erlotinib in these NSCLC models, establishing AXL over activation as a novel mechanism of mediating TKI treatment resistance. Small molecules targeting AXL are currently in clinical trials. BGB324, a selective ATP-competitive AXL inhibitor, was reported to inhibit AKT phosphorylation, decrease proinflammatory cytokines, and suppress cell invasion in AXL dependent breast cancer (Holland et al., 2010). BGB324 is now under a phase II clinical trial in patients with NSCLC refractory to anti-PD-L1 (NCT03184571). Dubermatinib (TP-0903), another potent inhibitor of AXL kinase, is under a phase Ia/Ib first-in-human, open-label, dose-escalation, safety, pharmacokinetic, and pharmacodynamic study (NCT02729298).

5.7. KRAS

KRAS is a guanosine triphosphatase (GTPase) that regulate signal transduction by cycling between active GTP-bound and inactive GDP-bound transition states. KRAS is one of the most frequent mutated gene in lung, colorectal, and pancreatic cancers (Kim et al., 2020). KRAS mutations are found in 20–25% of NSCLC, and in 32% of LUAD cases (Cancer Genome Atlas Research, 2014), often as substitutions involving codons G12, G13, and Q61 (Kim et al., 2020). KRAS G12C is the most frequent substitution, occurs in approximately 13% of NSCLC. A recent study from the European Thoracic Oncology Platform Lungscape Project reported that the specific G12C mutation is significantly associated with poorer prognosis among LUAD and in unselected NSCL patients (Finn et al., 2021).

For decades, KRAS oncoproteins have been classified as undruggable due to poor performance of KRAS inhibitors. Ostrem et al. (2013) first reported the discovery of inhibitors that bind irreversibly to KRAS G12C. This led to the identification of a new binding pocket, which opened up a new avenue of structure-based optimization of KRAS G12C inhibitors with increased potency, including ARS853, 1_AM, ARS1620, ARS3248, BI 1701963, GDC-6036, sotorasib (AMG510) and MRTX849. Among them, sotorasib and MRTX849 both were reported as potent, selective, and covalent KRASG12C inhibitors that selectively modify mutant cysteine 12 in GDP-bound KRASG12C, and inhibit KRAS-dependent signaling, with half-maximal growth inhibition concentration (IC50) values in the low nanomolar range and antitumor activity in xenograft mice model (Canon et al., 2019; Hallin et al., 2020). Sotorasib was further studied by Hong et al. (2020) in a phase I multicenter, open-label trial in patients with advanced solid tumors harboring the KRASG12C mutant protein. Of the 59 patients with NSCLC in the study cohort, 19 patients (32.2%) had a confirmed objective response (complete or partial

response) and 52 patients (88.1%) had disease control (objective response or stable disease), demonstrating encouraging anticancer activity. The identification and in-depth characterization of current and additional inhibitors, elucidation of their resistance mechanisms, and rational design of effective combinations will provide new insight toward KRAS dependence and the development of KRAS targeted therapy.

6. Immunotherapy

The host immune system plays an instrumental role in shaping the cancer landscape through immunoediting. The tumor cells can exploit multiple mechanisms to evade the immune surveillance and to foster an immune suppressive tumor microenvironment (Schreiber et al., 2011). Suppressive Tregs, myeloid derived suppressor cells (MDSCs), cytokines such as TGF-β and IL10, selection of cancer cells with defective antigen presenting machinery, immune tolerance conferred by expression of inhibitory checkpoint molecules like PD-L1 and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), and apoptosis of tumor reactive cells have all been implicated in evasion (Vinay et al., 2015). The goal and ongoing efforts of cancer immunotherapy are to counteract these mechanisms and reactivate the immune system to recognize and eliminate cancer cells. Among these, the application of ICB exampled by anti-PD1/PD-L1 has greatly improved the outcome of lung cancer treatment.

The PD1/PD-L1 pathway plays a dominant role in tumor immune evasion (Chen and Han, 2015). Blockade of the PD1/PD-L1 interaction using anti-PD1 or anti-PD-L1monoclonal antibodies have been shown to produce durable clinical benefit in patients with diverse advanced tumor types (Topalian et al., 2012; Brahmer et al., 2012). We summarize the clinical trials that led to the FDA approval of immune checkpoint inhibitors.

Pembrolizumab, a humanized antibody targets PD1, has been approved by the FDA to use as first-line treatment for patients with metastatic non-squamous NSCLC in combination with pemetrexed and carboplatin (Reck et al., 2016). It has also been approved as a first-line monotherapy for PD-L1 expressing NSCLC (≥50% staining as determined by an FDA approved test). The approval came after the success of two randomized, open-label, active-controlled trials that demonstrated statistically significant improvement in PFS and OS for patients received pembrolizumab compared with chemotherapy. In KeyNote-024, advanced NSCLC patients whose tumor cells are negative for sensitizing EGFR mutations or ALK translocations and positive for PD-L1 expression (≥50%) received pembrolizumab had a statistically significant improvement in OS and PFS (Reck et al., 2016). In KeyNote-010, in the total population, median OS was 10.4 months with 2 mg/kg pembrolizumab, 12.7 months with 10 mg/kg pembrolizumab, and 8.5 months with docetaxel. Among patients with at least 50% of tumor cells expressing PD-L1, pembrolizumab at 2 mg/kg significantly prolonged median OS from 8.2 months in docetaxel group to 14.9 months in patients received pembrolizumab; and with 10 mg/kg pembrolizumab, the median OS was extended to 17.3 months from that of 8.2 months in docetaxel group (Pai-Scherf et al., 2017; Herbst et al., 2016).

Nivolumab is another human monoclonal antibody against the PD1. The CheckMate-026 trial investigated the clinical benefit of nivolumab in the first-line setting vs. platinum-based doublet chemotherapy in patients with advanced NSCLC with positive PD-L1 (Carbone et al., 2017). The study revealed no significantly longer PFS with nivolumab than chemotherapy for patients with previously untreated stage IV or recurrent NSCLC, and that OS was similar between groups (Carbone et al., 2017). Nivolumab was further evaluated in combination with ipilimumab (a monoclonal antibody targeting CTLA-4) in CheckMate-227 trial for patients with stage IV or recurrent NSCLC (Hellmann et al., 2019), and it was concluded that nivolumab plus ipilimumab treatment prolongs the median OS from 13.9 months in patients with chemotherapy to 17.1 months in patients with nivolumab plus ipilimumab (Hellmann et al., 2019). Comparing the results of KeyNote-024 and CheckMate-026 trials, the pembrolizumab trial has implemented a more stringent PD-L1 expression criteria (50%) than that in the nivolumab study (5%), which may explain the discordance between the two studies. Therefore, PD-L1 expression holds a great promise as a predictive biomarker. And it still remains to be determined which population would benefit the most from ICB.

Atezolizumab was reported in a randomized, open-label, phase III trial (OAK) and shown to improve overall survival versus docetaxel in previously treated NSCLC (Rittmeyer et al., 2017). In the IMpower110 trial, 572 chemo-naive NSCLC patients with PD-L1 expression ≥1% were randomized 1:1 to receive atezolizumab or platinum-based chemotherapy, atezolizumab monotherapy resulted in significantly longer overall survival than platinum-based chemotherapy (Spigel et al., 2019; Herbst et al., 2020). Atezolizumab has been shown to confer prolonged PFS in first line setting in combination with bevacizumab plus chemotherapy in patients with metastatic nonsquamous chemotherapy naïve NSCLC patients (Socinski et al., 2018), and in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone (West et al., 2019; Jotte et al., 2020).

Durvalumab was reported to have no survival benefit in a phase III trial with or without tremelimumab, a fully human monoclonal antibody against CTLA-4, compared to standard chemotherapy in first-line treatment of metastatic NSCLC (Rizvi et al., 2020). It was then demonstrated in the PACIFIC trial to have durable PFS and sustained OS benefit in patients with unresectable, stage III NSCLC without disease progression after concurrent chemoradiotherapy (Antonia et al., 2018; Faivre-Finn et al., 2021; Gray et al., 2020).

Extensive work has been done in the validation and application of ICB in NSCLC immunotherapy. However, not all patients experience benefit with the current selection criteria. PD-L1 protein expression measured by IHC has been established as a predictive biomarker for ICB in the NSCLC Keynote clinical trials and in the setting of using pembrolizumab as first-line monotherapy in advanced NSCLC (Reck et al., 2016). In fact, this association between PD-L1 expression and response to therapy has been consistently observed in studies beyond lung cancer (Sunshine and Taube, 2015; Taube et al., 2014). Notably, many PD-L1 positive patients did not respond while a significant number of PD-L1 negative patients demonstrated responses in a retrospective analysis, arguing against the use of PD-L1 expression as a sole biomarker for patient selection. Rizvi et al. investigated the relationship of nonsynonymous mutation burden in tumors with the outcome of NSCLC patients treated with pembrolizumab, and revealed that a high nonsynonymous mutation burden was associated with improved objective response, durable clinical benefit, and progression-free survival (Rizvi et al., 2015). Since then, tumor mutation burden (TMB) has been extensively explored as a biomarker for response to ICB, and blood based TMB measurement has emerged as a promising alternative or complement approach to tumor based TMB (Samstein et al., 2019; Sholl et al., 2020). However, many challenges remain and current TMB analysis has not yet achieved unambiguous sensitivity or specificity for its clinical implementation (Sholl et al., 2020). PD1/PD-L1 pathway only represents one of many mechanisms among the signaling network and interplays between various immune components that the cancer cells may exploit to evade immune surveillance, it is thus imperative to identify and elucidate additional immune defects in the tumor microenvironment.

7. Conclusions and future perspectives

Neither SCLC nor NSCLC is a single disease but a collection of complex diseases with intertwined but unique molecular signatures that we just begin to appreciate. Optimal management of cancer demands that the cancerous tissue be screened for a list of predictive and prognostic biomarkers that guide treatment decision making. Targeting agents and biomarkers that are predictive for response or toxicity are now being identified and rationally designed to intervene particular mutations with a more streamlined clinical trial process. This is best exemplified by EGFR mutant NSCLC, where multiple generations of EGFR inhibitors have been

developed with accelerated approval of the third generation EGFR inhibitor osimertinib for the treatment of patients with metastatic EGFR T790M positive NSCLC; the subsequent acquired resistance to osimertinib again fueled the study of resistance mechanisms to the third generation EGFR inhibitors and the identification of EGFR C797S as the most common tertiary mutation and the development of fourth-generation EGFR inhibitors (Thress et al., 2015; Lu et al., 2018). Investigation of resistance mechanisms that are independent of EGFR further painted an even complex mutational landscape of NSCLC, including but not limited to MET alterations, HER2 amplification, RAS–MAPK and/or PI3K pathway activation, cell-cycle gene alterations, and oncogenic fusions (Leonetti et al., 2019), demonstrating the necessity of comprehensive mutation analysis and combination therapy for effective disease management. In sharp contrast to the remarkable progress that has been achieved in characterizing and targeting driver oncogenes in NSCLC, there has been little progress in development of molecularly targeted drugs for SCLC. It is thus imperative to deepen our understanding of SCLC tumor biology, identify and characterize distinct SCLC subtypes and their pertinent oncogenic pathways, to reveal their vulnerabilities and dependencies that can be exploited to maximize the benefits of existing and new approaches and expedite the process of drug development. Thanks to the continued accumulation of genomics, epigenetics and transcriptional data made available for SCLC, Rudin and colleagues summarized and proposed the existence of four distinct SCLC molecular subtypes, which can be marked by strong association of a prominent transcription factors with each subtype respectively: SLCL-A (*ASCL1*), SCLC-N (*NEUROD1*), SCLC-Y (*YAP1*), and SCLC-P (POU2F3) (Rudin et al., 2019). Simpson et al. (2020) reported the establishment of SCLC patient circulating tumor cell derived (CDX) mouse models, with the identification of an additional subtype marked by high expression of *ATOH1* and revealed double positive *ASCL1/NEUROD1* or *NEUROD1/ATOH1* tumors. The most recent advancement along this line was made by Gay et al. (2021), reporting the identification of four transcriptional distinct SCLC subtypes deduced from unbiased clustering of RNA-seq data from 81 SCLC patient samples, with three of the four subtypes being consistent with those defined by Rudin et al. (SLCL-A (ASCL1), SCLC-N (NEUROD1), SCLC-P (POU2F3), and the new fourth subtype defined by low expression of all three ASCL1/NEUROD1/POU2F3 transcription factor signatures accompanied by an Inflamed gene signature expression. Even more significantly, the four subtypes were found to have preferential vulnerabilities, with increased sensitivity of SCLC-A cells to BCL2 inhibitors, of SCLC-N cells to Aurora kinase inhibitors, of SCLC-P cells to PARP inhibitors, and of SCLC-I cells to the BTK inhibitor ibrutinib and with greatest benefit from the addition of immunotherapy to chemotherapy(129). Further validation and expansion of these preferential vulnerabilities in clinically relevant models will be a pivotal next-step, since it holds great potential for the development of biomarker-driven therapeutics and personalized treatment for SCLC. Looking forward, for both SCLC and NSCLC, the combination of molecular testing and targeting strategies tailored to tumor heterogeneity and resistance mechanisms is the key direction for future development.

Disclosure

The authors declare no conflict of interest.

Authors' contributions

All the authors contributed in the preparation of this work. Z.W. drafted and revised the manuscript; Z.W. and R.L. were responsible for the theme, final proof, and preparation of the manuscript for submission; J.K., P.Z., J.M.GA., Y.J, R.L. critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

References

Abel, S., Hasan, S., Horne, Z. D., Colonias, A., & Wegner, R. E. (2019). Stereotactic body radiation therapy in early-stage NSCLC: historical review, contemporary evidence and future implications. *Lung Cancer Manag., 8*, LMT09.

Akhurst, T. (2018). Staging of non-small-cell lung cancer. *Pet. Clin., 13*, 1–10.

Antonia, S. J., et al. (2018). Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N. Engl. J. Med., 379*, 2342–2350.

Araujo, J. M., Gomez, A. C., Pinto, J. A., Rolfo, C., & Raez, L. E. (2020). *Profile of Entrectinib in the Treatment of ROS1-Positive Non-small Cell Lung Cancer: Evidence to Date*. Hematol Oncol Stem Cell Ther.

Argiris, A., & Murren, J. R. (2001). Staging and clinical prognostic factors for small-cell lung cancer. *Cancer J., 7*, 437–447.

Awad, M. M., et al. (2013). Acquired resistance to crizotinib from a mutation in CD74-ROS1. *N. Engl. J. Med., 368*, 2395–2401.

Baltschukat, S., et al. (2019). Capmatinib (INC280) is active against models of non-small cell lung cancer and other cancer types with defined mechanisms of MET activation. *Clin. Cancer Res., 25*, 3164–3175.

Bargellini, I., Bozzi, E., Cioni, R., Parentini, B., & Bartolozzi, C. (2011). Radiofrequency ablation of lung tumours. *Insights Imaging, 2*, 567–576.

Bergethon, K., et al. (2012). ROS1 rearrangements define a unique molecular class of lung cancers. *J. Clin. Oncol., 30*, 863–870.

Black, R. C., & Khurshid, H. (2015). NSCLC: an update of driver mutations, their role in pathogenesis and clinical significance. *R. I. Med. J., 98*, 25–28, 2013.

Brahmer, J. R., et al. (2012). Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N. Engl. J. Med., 366*, 2455–2465.

Bray, F., et al. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J. Clin., 68*, 394–424.

Cancer Genome Atlas Research, N. (2012). Comprehensive genomic characterization of squamous cell lung cancers. *Nature, 489*, 519–525.

Cancer Genome Atlas Research, N. (2014). Comprehensive molecular profiling of lung adenocarcinoma. *Nature, 511*, 543–550.

Canon, J., et al. (2019). The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature, 575*, 217–223.

Carbone, D. P., et al. (2017). First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N. Engl. J. Med., 376*, 2415–2426.

Chen, L., & Han, X. (2015). Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. *J. Clin. Invest., 125*, 3384–3391.

Choi, Y. J., et al. (2021). Discovery of a novel CDK7 inhibitor YPN-005 in small cell lung cancer. *Eur. J. Pharmacol., 907*, 174298.

Christensen, C. L., et al. (2014). Targeting transcriptional addictions in small cell lung cancer with a covalent CDK7 inhibitor. *Cancer Cell, 26*, 909–922.

Clinical Lung Cancer Genome, P., & Network Genomic, M. (2013). A genomics-based classification of human lung tumors. *Sci. Transl. Med., 5*, Article 209ra153.

NCCN Clinical Practice Guidelines in Oncology, Small Cell Lung Cancer. (2022a). National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf.

NCCN Clinical Practice Guidelines in Oncology, Non-small Cell Lung Cancer. (2022b). National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Cross, D. A., et al. (2014). AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov., 4*, 1046–1061.

Doebele, R. C., et al. (2012). Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin. Cancer Res., 18*, 1472–1482.

Drilon, A., et al. (2018). Repotrectinib (TPX-0005) is a next-generation ROS1/TRK/ALK inhibitor that potently inhibits ROS1/TRK/ALK solvent- front mutations. *Cancer Discov., 8*, 1227–1236.

Dupuy, D. E., & Shulman, M. (2010). Current status of thermal ablation treatments for lung malignancies. *Semin. Intervent. Radiol., 27*, 268–275.

Entrectinib OK'd for Cancers with NTRK Fusions. (2019). *NSCLC. Cancer Discov* (vol. 9, p. OF2).

Faivre-Finn, C., et al. (2021). Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. *J. Thorac. Oncol., 16*, 860–867.

Farago, A. F., & Keane, F. K. (2018). Current standards for clinical management of small cell lung cancer. *Transl. Lung Cancer Res., 7*, 69–79.

Farago, A. F., et al. (2019). ATLANTIS: a Phase III study of lurbinectedin/doxorubicin versus topotecan or cyclophosphamide/doxorubicin/vincristine in patients with small-cell lung cancer who have failed one prior platinum-containing line. *Future Oncol., 15*, 231–239.

Finn, S. P., et al. (2021). Prognostic impact of KRAS G12C mutation in patients with NSCLC: results from the European thoracic Oncology Platform Lungscape project. *J. Thorac. Oncol., 16*, 990–1002.

Friboulet, L., et al. (2014). The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. *Cancer Discov., 4*, 662–673.

Fukuoka, M., et al. (2003). Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J. Clin. Oncol., 21*, 2237–2246.

Gainor, J. F., et al. (2016). Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov., 6*, 1118–1133.

Gay, C. M., et al. (2021). Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell, 39*, 346–360 e347.
Gazdar, A. F., Bunn, P. A., & Minna, J. D. (2017). Small-cell lung cancer: what we know, what we need to know and the path forward. *Nat. Rev. Cancer, 17*, 725–737.
Gelsomino, F., et al. (2014). Targeting the MET gene for the treatment of non-small-cell lung cancer. *Crit. Rev. Oncol. Hematol., 89*, 284–299.
George, J., et al. (2015). Comprehensive genomic profiles of small cell lung cancer. *Nature, 524*, 47–53.
George, J., et al. (2018). Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. *Nat. Commun., 9*, 1048.
Graham, R. P., et al. (2018). Worldwide frequency of commonly detected EGFR mutations. *Arch. Pathol. Lab Med., 142*, 163–167.
Gray, J. E., et al. (2020). Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC-update from PACIFIC. *J. Thorac. Oncol., 15*, 288–293.
Gristina, V., et al. (2020). The significance of epidermal growth factor receptor uncommon mutations in non-small cell lung cancer: a systematic review and critical appraisal. *Cancer Treat Rev., 85*, 101994.
Hallin, J., et al. (2020). The KRAS(G12C) inhibitor MRTX849 provides insight toward therapeutic susceptibility of KRAS-mutant cancers in mouse models and patients. *Cancer Discov., 10*, 54–71.
Haratake, N., & Seto, T. (2020). *NTRK Fusion-Positive Non-small-cell Lung Cancer: the Diagnosis and Targeted Therapy*. Clin Lung Cancer.
Hata, A., et al. (2015). Spatiotemporal T790M heterogeneity in individual patients with EGFR-mutant non-small-cell lung cancer after acquired resistance to EGFR-TKI. *J. Thorac. Oncol., 10*, 1553–1559.
Hellmann, M. D., et al. (2019). Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N. Engl. J. Med., 381*, 2020–2031.
Herbst, R. S., Morgensztern, D., & Boshoff, C. (2018). The biology and management of non-small cell lung cancer. *Nature, 553*, 446–454.
Herbst, R. S., et al. (2016). Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet, 387*, 1540–1550.
Herbst, R. S., et al. (2020). Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N. Engl. J. Med., 383*, 1328–1339.
Hipp, S., et al. (2020). A bispecific DLL3/CD3 IgG-like T-cell engaging antibody induces antitumor responses in small cell lung cancer. *Clin. Cancer Res., 26*, 5258–5268.
Holland, S. J., et al. (2010). R428, a selective small molecule inhibitor of Axl kinase, blocks tumor spread and prolongs survival in models of metastatic breast cancer. *Cancer Res., 70*, 1544–1554.
Hong, D. S., et al. (2020). KRAS(G12C) inhibition with sotorasib in advanced solid tumors. *N. Engl. J. Med., 383*, 1207–1217.
Horn, L., et al. (2018). First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N. Engl. J. Med., 379*, 2220–2229.
Howlader N, N. A., Krapcho, M., Miller, D., Brest, A., Yu, M., Ruhl, J., Tatalovich, Z., Mariotto, A., Lewis, D. R., Chen, H. S., Feuer, E. J., & Cronin, K. A. (Eds.). (2020). *SEER Cancer Statistics Review, 1975-2017*. Bethesda, MD: National Cancer Institute. based on November 2019 SEER data submission, posted to the SEER web site https://seer.cancer.gov/csr/1975_2017/.
Jotte, R., et al. (2020). Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized phase III trial. *J. Thorac. Oncol., 15*, 1351–1360.
Kalemkerian, G. P. (2012). Staging and imaging of small cell lung cancer. *Cancer Imag., 11*, 253–258.
Katayama, R., Lovly, C. M., & Shaw, A. T. (2015). Therapeutic targeting of anaplastic lymphoma kinase in lung cancer: a paradigm for precision cancer medicine. *Clin. Cancer Res., 21*, 2227–2235.
Kepp, O., Zitvogel, L., & Kroemer, G. (2020). Lurbinectedin: an FDA-approved inducer of immunogenic cell death for the treatment of small-cell lung cancer. *OncoImmunology, 9*, 1795995.
Khuder, S. A. (2001). Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Cancer, 31*, 139–148.
Kim, D., Xue, J. Y., & Lito, P. (2020). Targeting KRAS(G12C): from inhibitory mechanism to modulation of antitumor effects in patients. *Cell, 183*, 850–859.
Kobayashi, Y., & Mitsudomi, T. (2016). Not all epidermal growth factor receptor mutations in lung cancer are created equal: perspectives for individualized treatment strategy. *Cancer Sci., 107*, 1179–1186.
Kobayashi, S., et al. (2005). EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med., 352*, 786–792.
Kwak, E. L., et al. (2010). Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N. Engl. J. Med., 363*, 1693–1703.
Larotrectinib OK'd for Cancers with TRK Fusions. (2019). *Cancer Discov., 9*, 8–9.
Leonetti, A., et al. (2019). Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br. J. Cancer, 121*, 725–737.
Li, C., & Lu, H. (2018). Adenosquamous carcinoma of the lung. *OncoTargets Ther., 11*, 4829–4835.
Lu, X., et al. (2018). Targeting EGFR(L858R/T790M) and EGFR(L858R/T790M/C797S) resistance mutations in NSCLC: current developments in medicinal chemistry. *Med. Res. Rev., 38*, 1550–1581.
Lynch, T. J., et al. (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med., 350*, 2129–2139.
Malhotra, J., Malvezzi, M., Negri, E., La Vecchia, C., & Boffetta, P. (2016). Risk factors for lung cancer worldwide. *Eur. Respir. J., 48*, 889–902.
Markham, A. (2020). Tepotinib: first approval. *Drugs, 80*, 829–833.
Mitsudomi, T., et al. (2010). Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol., 11*, 121–128.
Mok, T. S., et al. (2017). Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N. Engl. J. Med., 376*, 629–640.
Nagasaka, M., et al. (2020). Beyond osimertinib: the development of 3(rd)-generation EGFR Tyrosine Kinase Inhibitors. *J. Thorac. Oncol., 16*(5), 740–763. https://doi.org/10.1016/j.jtho.2020.11.028. 33338652
Non-small Cell Lung Cancer Collaborative, G. (2000). *Chemotherapy for Non-small Cell Lung Cancer*. Cochrane Database Syst Rev, Article CD002139.
O'Leary, C., et al. (2020). Epidermal growth factor receptor (EGFR)-Mutated non-small-cell lung cancer (NSCLC). *Pharmaceuticals, 13*.
Ostrem, J. M., Peters, U., Sos, M. L., Wells, J. A., Shokat, K. M., & K-Ras. (2013). G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature, 503*, 548–551.
Pai-Scherf, L., et al. (2017). FDA approval summary: pembrolizumab for treatment of metastatic non-small cell lung cancer: first-line therapy and beyond. *Oncol., 22*, 1392–1399.
Papadopoulos, K. P., et al. (2020). U.S. Phase I first-in-human study of taletrectinib (DS-6051b/AB-106), a ROS1/TRK inhibitor, in patients with advanced solid tumors. *Clin. Cancer Res., 26*, 4785–4794.
Park, K., et al. (2021). Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS phase I study. *J. Clin. Oncol., 39*, 3391–3402.
Passaro, A., et al. (2021). Recent advances on the role of EGFR tyrosine kinase inhibitors in the management of NSCLC with uncommon, non exon 20 insertions, EGFR mutations. *J. Thorac. Oncol., 16*, 764–773.
Paz-Ares, L., et al. (2019). Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet, 394*, 1929–1939.
Pelosi, G., et al. (2015). Large cell carcinoma of the lung: a tumor in search of an author. A clinically oriented critical reappraisal. *Lung Cancer, 87*, 226–231.
Qin, A., & Kalemkerian, G. P. (2018). Treatment options for relapsed small-cell lung cancer: what progress have we made? *J. Oncol. Pract., 14*, 369–370.
Ragavan, M., & Das, M. (2020). Systemic therapy of extensive stage small cell lung cancer in the era of immunotherapy. *Curr. Treat. Options Oncol., 21*, 64.
Reck, M., et al. (2016). Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N. Engl. J. Med., 375*, 1823–1833.
Relli, V., Trerotola, M., Guerra, E., & Alberti, S. (2019). Abandoning the notion of non-small cell lung cancer. *Trends Mol. Med., 25*, 585–594.
Reungwetwattana, T., Liang, Y., Zhu, V., & Ou, S. I. (2017). The race to target MET exon 14 skipping alterations in non-small cell lung cancer: the Why, the How, the Who, the Unknown, and the Inevitable. *Lung Cancer, 103*, 27–37.
Riely, G. J., et al. (2021). Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with EGFR exon 20 insertion mutations from a phase I/II trial. *Cancer Discov., 11*, 1688–1699.
Rittmeyer, A., et al. (2017). Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet, 389*, 255–265.
Rizvi, N. A., et al. (2015). Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science, 348*, 124–128.
Rizvi, N. A., et al. (2020). Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non-small cell lung cancer: the MYSTIC phase 3 randomized clinical trial. *JAMA Oncol., 6*, 661–674.
Rosell, R., et al. (2012). Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol., 13*, 239–246.
Rudin, C. M., et al. (2019). Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. *Nat. Rev. Cancer, 19*, 289–297.
Samstein, R. M., et al. (2019). Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat. Genet., 51*, 202–206.
Schreiber, R. D., Old, L. J., & Smyth, M. J. (2011). Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science, 331*, 1565–1570.
Shaw, A. T., et al. (2014). Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N. Engl. J. Med., 371*, 1963–1971.
Shaw, A. T., et al. (2017). Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol., 18*, 1590–1599.
Shepherd, F. A. (2010). Surgery for limited stage small cell lung cancer: time to fish or cut bait. *J. Thorac. Oncol., 5*, 147–149.
Shepherd, F. A., et al. (2005). Erlotinib in previously treated non-small-cell lung cancer. *N. Engl. J. Med., 353*, 123–132.
Shepherd, F. A., et al. (2007). The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J. Thorac. Oncol., 2*, 1067–1077.
Sholl, L. M., et al. (2020). The promises and challenges of tumor mutation burden as an immunotherapy biomarker: a perspective from the international association for the study of lung cancer pathology committee. *J. Thorac. Oncol., 15*, 1409–1424.
Shun Lu, Q. W., Zhang, Guojun, Dong, Xiaorong, Yang, Cheng-Ta, Song, Yong, Chang, Gee-Chen, Lu, You, Pan, Hongming, Chiu, Chao-Hua, Wang, Zhehai, Feng, Jifeng, Zhou, Jianying, Xu, Xingxiang, Guo, Renhua, Chen, Jianhua, Yang, Haihua, Chen, Yuan, Zhuang, Yu, Shiah, Her-Shyong, Wang, Chin-Chou, Yang, Nong, Fang, Jian, Wang, Ping, Wang, Kai, Hu, Yanping, He, Jianxing,

Wang, Ziping, Shi, Jianhua, Chen, Shaoshui, Wu, Qiong, Sun, Changan, Li, Chuan, Wei, Hongying, Cheng, Ying, Su, Wu-Chou, Hsia, Te-Chun, Cui, Jiuwei, Sun, Yuping, & Hsin Yang, James Chih (2020). A multicenter, open-label, single-arm, phase II study: the third generation EGFR tyrosine kinase inhibitor almonertinib for pretreated EGFR T790M-positive locally advanced or metastatic non-small cell lung cancer (APOLLO), 16 Suppl. In , *vol. 80. Proceedings of the Annual Meeting of the American Association for Cancer Research 2020; 2020 Apr 27-28 and Jun 22-24. Philadelphia (PA): AACR; Cancer Res 2020. Abstract nr CT190.*.

Simpson, K. L., et al. (2020). A biobank of small cell lung cancer CDX models elucidates inter- and intratumoral phenotypic heterogeneity. *Nat. Can., 1*, 437–451.

Slotman, B., et al. (2007). Prophylactic cranial irradiation in extensive small-cell lung cancer. *N. Engl. J. Med., 357*, 664–672.

Socinski, M. A., et al. (2018). Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N. Engl. J. Med., 378*, 2288–2301.

Soda, M., et al. (2007). Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature, 448*, 561–566.

Soria, J. C., et al. (2018). Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N. Engl. J. Med., 378*, 113–125.

Spigel, F.d. M. D., Giaccone, G., Reinmuth, N., Vergnenegre, A., Barrios, C. H., Morise, M., Felip, E., Andric, Z. G., Geater, S., Özgüroğlu, M., Mocci, S., McCleland, M., Enquist, I., Komatsubara, K. M., Deng, Y., Kuriki, H., Wen, X., Jassem, J., & Herbst, R. S. (2019). LBA78 - IMpower110: interim overall survival (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1–selected NSCLC. *Ann. Oncol., 30*, v915.

Sun, S., Schiller, J. H., & Gazdar, A. F. (2007). Lung cancer in never smokers–a different disease. *Nat. Rev. Cancer, 7*, 778–790.

Sunshine, J., & Taube, J. M. (2015). PD-1/PD-L1 inhibitors. *Curr. Opin. Pharmacol., 23*, 32–38.

Syed, Y. Y. (2021). Amivantamab: first approval. *Drugs, 81*, 1349–1353.

Taube, J. M., et al. (2014). Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. *Clin. Cancer Res., 20*, 5064–5074.

Thress, K. S., et al. (2015). Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat. Med., 21*, 560–562.

Topalian, S. L., et al. (2012). Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med., 366*, 2443–2454.

Travis, W. D., et al. (2015). The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J. Thorac. Oncol., 10*, 1243–1260.

Tumbrink, H. L., Heimsoeth, A., & Sos, M. L. (2021). The next tier of EGFR resistance mutations in lung cancer. *Oncogene, 40*, 1–11.

Vallieres, E., et al. (2009). The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J. Thorac. Oncol., 4*, 1049–1059.

Vinay, D. S., et al. (2015). Immune evasion in cancer: mechanistic basis and therapeutic strategies. *Semin. Cancer Biol., 35*(Suppl. l), S185–S198.

Wang, S., Zimmermann, S., Parikh, K., Mansfield, A. S., & Adjei, A. A. (2019). Current diagnosis and management of small-cell lung cancer. *Mayo Clin. Proc., 94*, 1599–1622.

West, H., et al. (2019). Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol., 20*, 924–937.

Wu, Y. L., et al. (2017). Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol., 18*, 1454–1466.

Yang, J. C., et al. (2015a). Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol., 16*, 141–151.

Yang, J. C., et al. (2015b). Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol., 16*, 830–838.

Yang, J. C., et al. (2020). Safety, efficacy, and pharmacokinetics of almonertinib (HS-10296) in pretreated patients with EGFR-mutated advanced NSCLC: a multicenter, open-label, phase 1 trial. *J. Thorac. Oncol., 15*, 1907–1918.

Zhang, Z., et al. (2012). Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer. *Nat. Genet., 44*, 852–860.

Zhang, H., et al. (2020). CDK7 inhibition potentiates genome instability triggering anti-tumor immunity in small cell lung cancer. *Cancer Cell, 37*, 37–54 e39.

Zheng, M. (2016). Classification and pathology of lung cancer. *Surg. Oncol. Clin., 25*, 447–468.

Zheng, D., et al. (2017). EGFR G796D mutation mediates resistance to osimertinib. *Oncotarget, 8*, 49671–49679.

Zhou, C., et al. (2011). Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol., 12*, 735–742.